DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 81N-0060]

RIN 0905-AA06

Orally Administered Drug Products for the Treatment of Fever Blisters for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any over-the-counter (OTC) orally administered drug product for the treatment of fever blisters is not generally recognized as safe and effective and is misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on OTC orally administered drug products for the treatment of fever blisters that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: December 30, 1992.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 5, 1982 (47 FR 502), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC orally administered drug products for the treatment of fever blisters, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC orally administered drug products for the treatment of fever blisters was published in the **Federal Register** of June 17, 1985 (50 FR 25156). Interested persons were invited to file by August 16, 1985 written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by October 15, 1985. New data could have been submitted until June 17, 1986, and comments on the new data until August 18, 1986. Final agency action occurs with the publication of this final rule on OTC orally administered drug products for the treatment of fever blisters.

In the proposed rule, the agency did not propose any active ingredient for oral administration to treat fever blisters as generally recognized as safe and effective and not misbranded. However, the agency did propose monograph labeling in the event that data were submitted that resulted in the upgrading of any ingredients to monograph status in the final rule. The agency stated that in the event that new data submitted to the agency during the allotted 12-month comment and new data period were not sufficient to establish "monograph conditions" for OTC orally administered drug products for the treatment of fever blisters, the final rule would declare these products to be new drugs (50 FR 25156 at 25157). In this final rule, no active ingredient has been determined to be generally recognized as safe and effective for use in OTC drug products intended for oral administration to treat fever blisters. Therefore, proposed 21 CFR part 357, subpart H for OTC orally administered drug products for the treatment of fever blisters is not being issued as a final regulation.

This final rule declares OTC drug products containing active ingredients for oral administration to treat fever blisters to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), for which an application approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing these drugs for this use also would be misbranded under section 502 of the act (21 U.S.C. 352). In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application.

This final rule amends 21 CFR part 310 to include drug products containing active ingredients for oral administration to treat fever blisters by adding to subpart E new § 310.537 (21 CFR 310.537). The inclusion of OTC orally administered drug products for the treatment of fever blisters in part 310 is consistent with FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ 310.510, 310.519, 310.525, 310.526, 310.532, 310.533, and 310.534.) If, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC orally administered drug product for the treatment of fever blisters, the agency will promulgate an appropriate regulation at that time.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

In the proposed rule for OTC orally administered drug products for the treatment of fever blisters (50 FR 25156), the agency advised that it would provide a period of 12 months after the date of publication of the final monograph in the **Federal Register** for relabeling and reformulation of orally administered drug products for the treatment of fever blisters to be in compliance with the monograph. Although data and information were submitted on lysine in response to the proposed rule, they were not sufficient to support monograph conditions, and no monograph is being established at this time. Therefore, orally administered drug products for the treatment of fever blisters that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). In the advance notice of proposed rulemaking (47 FR 502 at 503), the agency advised that conditions for the drug products

subject to this monograph would be effective 6 months after the date of publication of a final monograph in the Federal Register. Because no OTC drug monograph is being established for this class of drug products, the agency is adopting this 6-month effective date for the nonmonograph conditions for these drug products. Therefore, on or after December 30, 1992, no OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application.

In response to the proposed rule on OTC orally administered drug products for the treatment of fever blisters, five physicians, one manufacturer, and one nutritionist submitted comments. No requests for oral hearing before the Commissioner were received. Copies of the comments received are on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. Comments on Lysine

1. Several comments supported the safety and effectiveness of L-lysine (hereinafter referred to as lysine) for the treatment of fever blisters. One comment submitted clinical data from published studies (Refs. 1 through 11), a 1986 unpublished study by Walsh et al. (Ref. 12), a summary of the data contained in references 1 through 12 (Ref. 13), a published letter (Ref. 14), a program for a symposium on lysine (Ref. 15), a summary of the symposium (Ref. 16), abstracts of presentations on lysine made at that symposium (Ref. 17), published data from in-vitro, animal, and human studies (Refs. 18 through 34), and patient information (Ref. 35). The comment subsequently provided the published results of the 1986 study by Walsh et al. (Ref. 36). Several other comments supported lysine's effectiveness for treating herpes simplex infections with anecdotal statements of treatment successes.

The agency has evaluated all of the data submitted but is discussing only references 1 through 12 and 36 specifically, because they are the only ones material to the in-vivo effectiveness of lysine. The agency does not consider these references as adequately demonstrating that lysine is generally recognized as safe and effective for OTC drug use in relieving the discomfort of fever blisters and cold sores.

Kagan (Ref. 1) stated that eight subjects with facial herpes and two with genital herpes were treated with 390 milligrams (mg) of lysine. This dosage, given at the first evidence of herpetic lesions, was continued for 5 days and the results were reported as "uniform, rapid resolution of lesions." No other specific information was given. This study was not a placebo-controlled study and contains insufficient data on which to base any conclusion.

Griffith, Norins, and Kagan (Ref. 2) reported results of an uncontrolled, open study on 45 volunteers, 11 male and 34 female, 4 to 60 years of age with a history of recurrent fever blisters. The daily dosage of lysine for subjects with active infections was 800 to 1,000 mg/day compared with a maintenance dose of 312 to 500 mg/day. Cereals, seeds, nuts, chocolate, and other foods which were noted to produce a high arginine-to-lysine ratio and to favor herpetic lesions were curtailed in the diet. Infections were described as mild in 6 subjects, moderate in 33 subjects, severe in 4 subjects, and incapacitating in 2 subjects. Two treatment failures were reported, both of which occurred in the mildly-infected subjects. Though three of the subjects were lost to followup, the followup period for the others was 2 months to 3 years. Pain was reported as disappearing overnight in virtually every instance and more rapidly than with past treatments. Recurrences were reported to show decreased frequency. However, the results were considered suppressive rather than curative because when lysine was discontinued after the subjects had been maintained on lysine infection-free for 2 months to 3 years, the lesions recurred in 1 to 4 weeks.

The study was not placebo-controlled; therefore, it does not meet agency requirements for evaluation. The agency has carefully evaluated all of the data in this study and concludes that lysine's effectiveness in relieving the discomfort of fever blisters was not adequately demonstrated.

Milman, Scheibel, and Jessen (Ref. 3) reported results of a randomized, double-blind, placebo-controlled study conducted for 48 weeks in 119 subjects, 103 of whom were females aged 16 to 60 years (median age of 36 years), with herpes infections. Enrollment was restricted to otherwise healthy people who had had at least three herpes simplex episodes in the preceding year. Only subjects with prolabial and perioral lesions were enrolled and diagnosis was based on a thorough history, though in some cases the lesions were seen on examination by the investigators.

The subjects were given either 11 lysine tablets (500 mg) or 11 placebo tablets on the initial visit and instructed to take two tablets at the onset of a lesion, followed by one tablet each subsequent morning and evening until the tablets were gone. The subjects were to return after each episode, at which time a questionnaire was filled out regarding symptoms and findings, and the residual tablets were to be returned. A new questionnaire and a new box of medication were given at that time. Treatment with followup was carried out for 251 episodes of recurrent herpes simplex (prolabial or perioral sites).

Analysis of results was made for only those episodes for which treatment was started on the day the first symptom(s) appeared. Sixty-one episodes were excluded (29 lysine and 32 placebo). Exclusion was based on the following criteria: (1) treatment was not started on the day the first symptoms appeared; (2) the subject returned more than two tablets; or (3) the data were inadequate.

Median recurrence-free intervals in lysine and placebo-treated groups were 57 (8 to 185) days and 53 (11 to 154) days, respectively. Subjects were assessed for rate of healing and the appearance of the lesion at its worst. The healing rate (median days) for initial treatment was 8 (1 to 24) days for lysine, and 7 (1 to 17) days for placebo. The healing rate for all treatments was 8 (1 to 31) days for lysine and 8 (1 to 17) days for placebo. According to these data, the healing rate for placebo seems better than the rate for lysine.

The results for this study were reported as showing no difference between placebo and lysine treatment for the rate of healing and the appearance of the lesion at its worst. "No effect" for lysine treatment (500 mg twice a day) was seen in recurrent herpes labialis. Accordingly, this study cannot be used to demonstrate lysine's effectiveness in relieving the discomfort of fever blisters.

The authors commented that the dose of lysine in this study may have been too low. They also note that because virus multiplication in the herpetic lesion begins in the prodromal stage, therapy must begin immediately when symptoms develop.

Saunders (Ref. 4) reported that 40 subjects with oral or genital herpes were treated with maintenance doses of lysine daily resulting in 34 subjects who showed either shorter duration of episodes, diminished frequency (from 50 percent to total remission), or both.

Concomitant iododeoxyuridine ointment was also used. The treatment was not placebo controlled, and no data were included. The agency considers the information provided as insufficient for evaluation.

Milman, Sheibel, and Jessen (Ref. 5) conducted a double-blind, placebo-controlled, crossover study to test the following hypothesis: In recurrent herpetic lesions, virus multiplication begins in the prodromal stage and is maximal during the following 24 hours with subsequent rapid decline. Thus, treatment must be initiated immediately at the onset of the first symptoms.

The study population consisted of healthy volunteers with at least three perioral and/or prolabial herpes simplex episodes in the preceding 12 months. On the first visit, subjects were given a questionnaire and tablets containing 500 mg lysine monohydrochloride or placebo. The subjects were instructed to take one tablet twice daily during the entire study and to record on their questionnaires the duration and course of their herpes simplex recurrences and to classify the lesion, when at its worst, according to the following scale: (1) itching, burning, tingling, or tenderness but no visible lesion; (2) erythema with induration (papule) and/or vesicles without exudation; (3) vesicles with exudation and/or crust, lesion 15 millimeters (mm) or less, measured along the largest diameter; (4) vesicles with exudation and/or crust, lesions greater than 15 mm. These questionnaires were to be mailed in, along with any remaining medication, at 4-week intervals; then new questionnaires and a fresh supply of tablets were issued. Crossover, without interruption in the study, was made at 12 weeks. Sixty-five subjects (52 females, 13 males), aged 16 to 73 years (median age 36 years), completed the study.

Subjects initially treated with lysine had 45 recurrences during lysine and 38 recurrences during placebo treatment. Subjects initially treated with placebo had 66 recurrences during placebo and 46 recurrences during lysine treatment. The total number of recurrences during lysine treatment was 91, and during placebo treatment 104. The agency has determined that none of these differences was statistically significant and that there are no significant differences between the lysine and placebo treatment series as regards the rate of healing and the appearance of the recorded herpes lesions at their worst.

The authors also reported that significantly more subjects were recurrence-free during lysine than during placebo treatment. While this finding might suggest an effect of lysine in some of the subjects, it does not establish effectiveness.

The agency also notes that subjects initially treated with placebo had 66 recurrences during placebo, whereas subjects initially treated with lysine had 38 recurrences during placebo treatment. The agency finds that this is a marked difference and might be interpreted as showing that lysine given initially was effective during the subsequent placebo period.

The authors concluded that lysine had no significant prophylactic effect, either on the duration or on the recurrence rate of herpes simplex labialis. However, the results suggest that certain people may benefit from such treatment, and further investigations are indicated to clarify this hypothesis.

Walsh, Griffith, and Behforooz (Ref. 6) tested the effect of lysine supplementation on herpes infection. Their study design was a retrospective questionnaire which constituted an "epidemiological survey." Over a 3-month period, at 300 randomly selected retail general nutrition stores, self-addressed reply post card questionnaires were distributed to purchasers of lysine. Individuals with herpes infection who wished to participate in a medical survey were asked to return the postcard. Eventually, 4,000 questionnaires were sent out, with 1,543 respondents (38 percent); 1,043 (67 percent) were female and 500 (33 percent) were male. Data gathered from the questionnaires described the survey population, types of herpes, frequency of attacks, effect of other forms of therapy tried, and the effect of lysine on herpes infection. Fifty-four percent of the survey population reported that they had been treated for herpes by a physician. Of these, 16 percent reported that cultures had been obtained with 72 percent of the cultures giving positive results. The most frequent diagnoses reported were: (1) cold sores (50 percent), (2) cold sores and canker sores (17 percent), (3) genital herpes (11 percent), (4) canker sores alone (11 percent), and (5) shingles and various combinations of herpes (less than 10 percent of the subjects). Frequency of infection in subjects with cold sores was reported as four or less times a year in 47 percent of the subjects, five to eight times per year in 37 percent, and more than eight times per year in 16 percent. Ten percent of the subjects showed healing in 5 days when they were untreated compared to 73 percent who showed healing in the same period when they were treated. The percentage of subjects with severe symptoms decreased from 59 percent to 7 percent with lysine, subjects with moderate symptoms increased from 18 percent without treatment to 27 percent with treatment. Those with mild symptoms increased from 3 percent without therapy to 65 percent with lysine treatment, and subjects with intolerable symptoms decreased from 20 percent without treatment to 1 percent with treatment. During the period of treatment with lysine, recurrence was reportedly prevented in 35 percent, decreased in 49 percent, and was unchanged in 16 percent of the total subject population. Severity of symptoms, time required for healing, and frequency of recurrences were all reported as decreased in subjects who supplemented their diets with lysine.

The usual dosage of lysine reported by the respondents for this study was three tablets (936 mg/day). Subjects with cold sores reportedly averaged 2 to 3 lysine tablets (780 mg/day).

The authors noted that prior to the time of their publication no extensive double-blind study had been published testing the therapeutic value of lysine for the treatment of herpes infection. They concluded that the results of this survey demonstrated sufficient potential to encourage more definitive studies on the efficacy of supplemental lysine for the treatment of herpes viral infections.

The agency finds that this study does not establish effectiveness for the following reasons: (1) it was a retrospective, epidemiological survey, based on responses to a questionnaire and was not a double-blind, placebo-controlled, or prospective clinical trial; (2) because the study did not include subjects treated with a placebo, the study objectives could not be achieved; (3) there was no particular setting at which the subjects were treated (only 54 percent of the population stated that "at some time" they had been treated for herpes by a physician); (4) the diagnoses were varied for the study population and included cold sores, cold sores and canker sores, canker sores alone, genital herpes, shingles, and various combinations of herpes (there should have been a uniform population of subjects with fever blisters and cold sores only for the indication desired in this rulemaking); (5) the dosages used by the participants in this study varied: 3 tablets of lysine (936 mg/day) was the usual dosage, while subjects with cold sores reported an average dosage of 2 to 3 lysine tablets (780 mg/day); (6) none of the study participants was examined by the investigators for measurements of lesion size, or for the presence of vesicles or crusting; (7) admissibility

and exclusion criteria which might influence the response of the subject are not mentioned, e.g., good health, hypersensitivity history, concomitant medication, skin creams, or food products (e.g., milk products); and (8) study subjects should be able to adhere to a study protocol (e.g., take the drug and report daily for examination as required by the protocol). Certain variables should be considered in the pre-episode period: the distance of the subject from the clinical facility and the person's ability to come to the facility on a daily basis during an episode of a fever blister should be determined at this time.

Because of these problems, this study cannot be used to demonstrate lysine's effectiveness in relieving the discomfort of fever blisters or cold sores.

DiGiovanna and Blank (Ref. 7) conducted a randomized, placebo-controlled, double-blind study to determine whether lysine can modify or prevent clinical recurrences of *herpes simplex* virus infections. There were 21 subjects (10 lysine, 10 placebo, and 1 untreated due to spontaneous remission and failure to have further episodes of *herpes simplex* virus infection during the study). Subjects enrolled in this study were volunteers in good health with a history of herpes simplex infections recurring at least every 6 weeks and without previous therapy with lysine. After the diagnosis of herpes simplex was made based on clinical examination by one of the investigators and a positive Tzanck smear for abnormal cytologic findings was obtained, the subjects were randomly assigned in a double-blind fashion to either the placebo or lysine treatment group. Treatment consisted of 400 mg lysine oral capsules or placebo (lactose) capsules given three times daily for 4 to 5 months. Patients were given a 1-month supply of capsules on admission to the study. The instructions given at that time were that the capsules should only be taken when prodromal symptoms or a lesion appeared, and the medication should be continued for the duration of the study. Subjects were instructed to keep records of the date of onset of the prodrome, date of appearance of the first visible lesion, the number of individual lesions (single vesicles or papules), and the date of healing (day when the crust came off without bleeding or reforming). The subjects were to bring this information with them for review at the time of their monthly medical visits. At this time, they were given another month's supply of medication. During this study, limitation of foods high in arginine (seeds, nuts, chocolate, etc.) was advised.

In both groups, the subjects had lesions more than 40 percent of the time. This was believed to be affected by the admission criteria. There was no substantial difference in the frequency or duration of episodes and no difference in the number of lesions per episode between the two groups.

The investigators concluded that there was no significant difference between the lysine and placebo groups in episode frequency, duration, or severity. They were unable to substantiate any statistically significant effect of lysine in the treatment or prophylaxis of recurrent *herpes simplex* virus infection. They felt that this conclusion was valid despite the small number of subjects. The agency concurs that the results do not support effectiveness.

McCune, et al. (Ref. 8) studied the effect of oral lysine treatment on the severity, duration, and recurrence of symptoms and lesions in nonimmunocompromised subjects with *herpes simplex* virus infection. This was a prospective, randomized, double-blind, placebo-controlled crossover study with 41 evaluable subjects. In contrast to a number of other studies, the subjects in this study were diagnosed with culture proven *herpes simplex* virus infection at the time when they were enrolled in the study, but were not differentiated as Type 1 or Type 2 by viral subtyping. The subjects were in general good health except for their history of recurrent *herpes simplex* virus infection with at least 3 episodes in the preceding 6 months.

Each subject was seen by one investigator on entry into the study and at 12, 24, 36, and 48 weeks of treatment. A questionnaire was completed by each subject at each visit and reviewed by the investigator. The protocol recommended a dietary limitation of foods high in arginine content (peas, cereals, peanuts, cashews, cola drinks, beer (barley), and chocolate). Foods high in lysine content were encouraged (dairy products, milk, potatoes, Brewer's yeast). Subjects received either two or four 312 mg lysine tablets.

In 98 percent of the subjects, complete healing (time to loss of crust) of *herpes simplex* virus infection occurred within 2 weeks after the onset of the acute episode, and 71 percent noted healing in less than 9 days. Decreased recurrence rate occurred in nonimmunocompromised subjects treated with oral lysine tablets—four 312 mg tablets/day. A dose of 624 mg/day (one 312 mg tablet twice daily) was noted as not effective.

The agency believes that the data show that lysine may be capable of decreasing the severity of symptoms associated with *herpes simplex* virus recurrences; however, neither dosage shortened healing time when compared with placebo.

Because animal models have shown that oral lysine can alter intracellular sodium and potassium levels without detectable serum changes, serum sodium and chloride levels were checked in each subject at baseline examination and at each 12-week recheck examination. No subject was on supplemental oral potassium treatment or receiving any other medication which could change the serum levels of these electrolytes. No abnormalities were detected at baseline or during followup, and there were no complaints of weakness, ataxia, or muscle tremors.

A major deficiency of this study was the failure to have the subjects come in for daily evaluation for the first 8 days or at some specified time during the first 8 days after the onset of the fever blister. The guidelines recommended by the Panel stress this requirement and note that one of the criteria for admissibility and exclusion is that the subjects should be able to comprehend instructions and adhere to the study protocol (e.g., take the drug and report daily for examination as required).

The Panel's guidelines also restrict the use of other medications, skin creams, or food products (e.g., milk products) that might influence the response of the subject in the study. In this study, dairy products were encouraged as foods that were high in lysine content, and foods high in arginine content were discouraged.

The data concerning the duration of fever blisters and the duration of symptoms were not given in actual number of days, but were recorded as either healing in or lasting for more than 5 days.

Information was collected by questionnaires which the subjects completed at each visit to the investigator. These subjects were seen by the investigator on one pretreatment visit, and then at 3-month intervals at 12, 24, 36, and 48 weeks. The agency believes that information collected at these protracted intervals will not be as accurate as information collected daily, or at much more frequent periods. Based on these deficiencies, this study cannot be used to demonstrate lysine's effectiveness in relieving the discomfort of fever blisters and cold sores.

Miller and Foulke (Ref. 9) reviewed studies concerned with the roles of arginine and lysine in *herpes simplex*

virus replication and the mechanisms by which lysine seems to antagonize arginine. The authors reached the following conclusions: (1) treatment of *herpes simplex* virus infections should involve curtailment of arginine intake and increased lysine intake; (2) the ratio of lysine to arginine in a person's diet is a critical factor in prevention of recurrent *herpes simplex* virus infection. Tables are given listing the lysine/arginine ratio for foods high in lysine (milk, fish, chicken, beef, pork, Brewer's yeast, soybeans, and legumes) and for foods high in arginine (nuts, chocolate, popcorn, jello, gelatin, brown sugar, raisins, seeds, whole wheat bread); (3) if people restrict arginine intake during lysine treatment of an active episode of *herpes simplex* virus infection, the size and the duration of lesions can be decreased; (4) lysine only suppresses virus infections, it does not cure; (5) though lysine halts herpetic replication, it has no role in the healing process; and (6) some people have controlled recurrence by merely limiting their dietary intake of foods high in arginine content.

These authors also studied nine subjects with recurrent oral *herpes simplex* virus over a period of 8 months. An arginine-restricted diet was prescribed, and lysine hydrochloride 500 mg was given each day. The results reported were smaller lesions of shorter duration (2 to 5 days versus 7 to 10 days in the past). The authors concluded that further clinical studies are needed, including double-blind placebo-controlled studies with and without arginine limitation.

The agency finds that this study cannot be used to demonstrate lysine's effectiveness in relieving discomfort of fever blisters and cold sores because it was not placebo-controlled.

Thein and Hurt (Ref. 10) conducted a randomized, double-blind, placebo-controlled, crossover study of 26 subjects (3 male and 23 female), aged 8 to 50 years (median age 29 years), to investigate why people who have circulating antibodies to *herpes simplex* virus 1 do not suffer from recurrent lesions. They examined the efficacy of long-term prophylactic lysine supplementation, with dietary arginine reduction, and the relationship of serum amino acid concentrations to the frequency of herpetic lesions. The subjects were divided into two groups (A–15 subjects and B–11 subjects) and given either lysine 1,000 mg or placebo daily for 6 months. The subjects were then crossed over to the opposite treatment for another 6 months. The criteria for acceptance into this study required subjects to be healthy except for a history of at least three episodes of circumoral herpes lesions in the preceding year. A baseline history, physical examination, data concerning herpetic lesion history, and information concerning dietary habits were obtained. Blood samples were obtained pretreatment, and at the 6-month and 12-month visits. Journals were distributed at the pretreatment and 6-month visits for recording of information pertinent to herpetic episodes throughout the study. Each participant was given a 6-month supply of the active drug (500 mg lysine tablets) or placebo. The dosage was two tablets each morning before breakfast.

After the study began, each participant was to contact the authors at the next appearance of a lesion, in order to permit a positive diagnosis of recurrent herpes simplex labialis. After 52 weeks, the study was terminated. All previously obtained and frozen serum samples were analyzed for levels of lysine and arginine, a lysine:arginine ratio was computed, and the significance between sample means was determined.

The two test groups were rated as comparable during the first 6-month period with regard to recurrences. The investigators concluded that the frequency of recurrences of herpetic lesions appeared to correlate with the serum levels of lysine. Those with elevated serum levels had fewer recurrences than those with serum levels less than 165 nanomols per milliliter (nmols/mL).

The agency notes that the study results showed that, during the first 6 months of the study, the subjects initially given placebo (Group B) showed a steadily rising increase in serum lysine concentration which nearly equalled the increase demonstrated by the subjects who were receiving lysine supplementation (Group A). When the Group B subjects were given lysine for the second 6-month period of the study, their serum lysine levels continued to increase at an even more rapid rate. The lysine-arginine concentration ratio also showed a consistent increase for both Groups A and B, with Group B exceeding Group A for about the last one-third of the first 6 months, and continuing to increase during the second 6 months, whereas the Group A subjects showed a decrease in this ratio when they were started on the placebo portion of the study for the second 6-month period. In this study, dietary arginine restriction was recommended. The role of diet in these findings cannot be assessed because dietary intake is not explicitly itemized. This is the only study submitted which measured serum for lysine and arginine concentrations. The agency believes it would be necessary to have some replication of these findings in order to consider the results conclusive.

Simon, Van Melle, and Ramelet (Ref. 11) described a randomized, double-blind study comparing episodes of herpes simplex labialis or herpes simplex genitalis in 31 subjects treated with either lysine or mannitol capsules (250 mg/capsule). For inclusion in this study, subjects were required to have a history of at least 4 (average was 9.7) annual episodes of herpes simplex labialis or genitalis infections. After the initial visit, at which time the treatment regimen was randomly assigned, the subjects were seen at 3 and 6 months. In the interim periods, they recorded the severity and duration of each recurrence.

The dosage used for the first trimester was 1,000 mg daily. During the second trimester, subjects were given 250 mg each morning and 500 mg at night for a total dosage of 750 mg each day.

The 15 placebo subjects were reported to have approximately a 25-percent reduction in the expected number of recurrences during both trimesters of treatment. The 16 subjects in the lysine group, after correction for placebo effect, were reported to experience a 47 percent reduction in recurrences during the first trimester, but during the second trimester showed a less beneficial effect than was noted for the placebo subjects.

The authors concluded that there was a dose-related effect with lysine treatment based on the differences between the first and second trimester results. The authors stated that further studies are needed at doses of more than 1,000 mg/day before dismissing lysine treatment in the prophylaxis of recurrent *herpes simplex* infection.

Walsh, et al. (Refs. 12 and 36) conducted a double-blind, placebo-controlled, randomized study over a 6-month period of 114 subjects (29 male and 85 female) who had at least two episodes of *herpes simplex* virus infection in the 6 months preceding the study period. The subjects were randomly assigned to a lysine or placebo group.

Of the evaluable subjects, 27 (6 male and 21 female) received lysine (1,000 mg three times a day) and 25 (6 male and 19 female) received placebo. The subjects were examined pre-treatment, at 3 months, and at 6 months at the end of the trial. On the initial visit, the participating physician gave the subjects a 6-month supply of tablets with instructions to take two tablets three

times a day with meals. The subjects were also advised to avoid foods containing large amounts of arginine such as nuts, chocolate, and gelatin. Each subject was to record the occurrence, severity, and duration of herpes attacks for the 6-month study period.

The participating physicians completed followup forms at 3 and 6 months. The information included subject compliance, number of *herpes simplex* virus attacks, severity of attacks, healing time, symptoms, and the subjects' perceived effectiveness of the treatment.

The investigators evaluated results for expected outcomes based on the subjects' recall of their herpes simplex virus attacks for the 6 months preceding the study as well as the actual outcomes for this study. Subjects rated their overall experience during the trial with the 6 months just prior to the trial. The subjects who received lysine reported the treatment was either "effective" or "very effective," whereas only 28 percent of the subjects who received placebo reported lysine as "effective" or "very effective." The subjects who received lysine reported shorter healing time, fewer attacks, and milder symptoms when compared with the subjects who received placebo. No significant adverse effects were reported.

The agency finds a number of deficiencies with this study: (1) lack of information concerning the qualifications of the participating physicians or their study settings; (2) the dosage of lysine used in this study is much higher than the dosage used in any of the other studies submitted, which may explain the improved results reported; (3) none of the subjects was actually seen by the investigators; (4) subjects were advised to avoid foods known to contain large amounts of arginine (nuts, chocolate, and gelatin). The effect of diet cannot be assessed because too little information is available concerning the actual dietary intake of the participants; and (5) there should be a breakdown of the data so that the data for genital herpes would be separate from the data for oral herpes.

In summary, only seven of the studies were described as placebo-controlled, randomized, and double-blind (Refs. 3, 5, 7, 8, 10, 11, 12, and 36). The data for these studies were obtained in the following ways: (1) from questionnaires mailed to the investigators (Ref. 5), (2) from questionnaires filled out at the time of the revisit to the investigator (Refs. 3 and 8), and (3) from journals kept by the subjects and which were reviewed at the scheduled followup visits at various monthly intervals (Refs. 7, 10, 11, 12, and 36).

The results reported by these investigators can be summarized as follows: (1) there was no difference between lysine and placebo for the rate of healing and the appearance of the lesion at its worse (Refs. 3 and 5); (2) there was no significant difference in the frequency, duration, or severity of the infectious episodes when lysine and placebo results were compared (Ref. 7); (3) the recurrence rate was decreased by the 1,248 mg/day dosage of lysine, but not by the 624 mg/day dosage; neither dosage shortened healing time when compared with placebo; lysine treatment was recommended with reservation due to the small sample size and because of variable factors such as spontaneous cures and placebo effect (Ref. 8); (4) the frequency of occurrences correlated with the serum levels of lysine; lesions were suppressed when lysine was present at levels equal to or greater than 165 nmols/mL (Ref. 10); (5) there was a dose-related effect for recurrences; no effect was seen at 750 mg/day but recurrences were decreased at the dosage of 1,000 mg/day (Ref. 11); and (6) lysine was noted to reduce the frequency, increase the healing rate, and decrease the severity of symptoms (Refs. 12 and 36).

Three of these studies reported no significant difference between placebo and lysine, two reported a dose-related effect, one reported a decrease in the frequency of recurrences when serum levels for lysine were at least 165 nmols/mL, and only one (Refs. 12 and 36) reported unequivocal superiority of lysine treatment when compared with placebo.

The agency concludes that those studies that are not placebo-controlled do not meet the basic agency criteria that require the drug under investigation be shown to be more effective than placebo in relieving the discomfort, shortening the duration, or decreasing the frequency of fever blisters or cold sores. Study protocols should require the study subjects to return to the investigator or an assistant for examination of the herpes lesions within 24 hours after the lesion first occurs, and for interview and examination daily for the 8-day period after onset of the lesion. At each of these visits, the subjects should have lesions examined for vesicles, dry crust, and size. They should also be evaluated for discomfort on a preselected scale for the preceding 24 hours. When claims are to be made for decreased duration of lesions, the number of days must be given from onset of the lesion(s) to the time of healing (crust falling off). When claims are to be made for decreased frequency of lesions, the number of days must be given from the time of healing of the lesion(s) until the time of recurrence of lesions. Because so many investigators stress the importance of diet as a source of lysine and arginine, diet as a variable needs to be prescribed and monitored in a manner which would create greater consistency from one study to another. In order to compare studies with one another, the dosages of lysine should be comparable. Subjects with genital herpes should be evaluated separately from oral-facial herpes, and dosages should be given separately for these subjects. Genital herpes is currently not included as an acceptable claim in this OTC drug review rulemaking. Further studies are needed before evaluation can be made of the significance of serum concentrations of 165 nmols/mL of lysine as an indicator of lysine's effectiveness. Anecdotal information in the form of testimonial comments is not adequate to establish lysine's effectiveness in treatment of fever blisters. (See 21 CFR 330.10(a)(4)(ii).)

Because the agency finds all of the submitted studies are deficient in one or more essential items as discussed above, the data are not adequate for lysine to be considered generally recognized as safe and effective for OTC drug use for oral administration in the treatment of fever blisters and cold sores.

The agency's detailed comments on the data are on file in the Dockets Management Branch (Ref. 37).

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(13) Table: Summary of Studies in References 1 through 12, in Tab 16, Comment C00004, Docket No. 81N–0060, Dockets Management Branch.

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(15) Program for Symposium on L-Lysine for the Treatment of Herpes Infections, sponsored by Indiana University School of Medicine, October 14, 1985, in Tab 17, Comment No. C00004, Docket No. 81N–0060, Dockets Management Branch.

(16) Summary of the October 14, 1985 Symposium on L-Lysine for the Treatment of Herpes Infections, in Tab 18, Comment No. C00004, Docket No. 81N–0060, Dockets Management Branch.

(17) Abstracts of the Presentations at the October 14, 1985 Symposium on L-Lysine for the Treatment of Herpes Infections, in Tab 19, Comment No. C00004, Docket No. 81N–0060, Dockets Management Branch.

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(36) Griffith, R., et al., "Success of L-Lysine Therapy in Frequently Recurrent Herpes Simplex Infection, Treatment and Prophylaxis," *Dermatologica*, 175:183–190, 1987.

(37) Letter from W. E. Gilbertson, FDA, to R. S. Griffith, coded LET4, Docket No. 81N–0060, Dockets Management Branch.

2. Two comments stated their belief that, if lysine was found safe and effective in the prophylaxis and treatment of fever blisters, there would be enough interest generated in the various viral research centers to study and evaluate lysine in more serious herpes virus infections, such as genital herpes, shingles, and infectious mononucleosis. One comment stated that lysine may have a role in anticancer therapy since arginine stimulates and lysine inhibits certain tumor viruses. The second comment described an animal study in which "tumor implants grow faster with arginine and that lysine antagonizes or prevents tumor growth." The comment added that this study should be verified because lysine may have value as adjunctive therapy in human tumors.

One of the comments suggested that lysine be evaluated as an additive to enhance the effectiveness of other antiviral agents such as acyclovir. The other comment added that lysine's role in the treatment of conditions which may be related to herpes infections, such as Bell's palsy, also warrants evaluation.

The uses of lysine in more serious herpes infections, as mentioned by the comments, are outside the scope of this rulemaking for OTC drug products used for the treatment of fever blisters. Therefore, they will not be discussed further in this document. Persons interested in studying lysine for those uses should follow the investigational new drug procedures. (See 21 CFR Part 312.)

B. Comment on Lactobacillus Acidophilus and Lactobacillus Bulgaricus

3. One comment stated that data from its clinical studies on a product containing *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* failed to provide convincing evidence of efficacy (Ref. 1). Accordingly, the comment voluntarily decided to drop the claim that this product is helpful in relieving the discomfort associated with fever blisters (Ref. 2).

REFERENCES

(1) Comment No. C00003, Docket No. 81N–0060, Dockets Management Branch.

(2) Comment No. SUP1, Docket No. 81N–0060, Dockets Management Branch.

C. Comment on Labeling

4. One comment discussed suggested labeling for OTC lysine drug products. Because lysine has been classified as a nonmonograph ingredient in this final rule for OTC orally administered drug products for the treatment of fever blisters, the agency is not addressing the comment's request. Data in the form of a new drug application or a petition to establish a monograph, pursuant to 21 CFR 10.30, may be submitted to support lysine's effectiveness for the treatment of fever blisters and cold sores. Should such data demonstrate lysine's effectiveness in treating fever blisters and cold sores, the agency will then consider labeling recommendations such as those made by the comment.

II. The Agency's Final Conclusions on OTC Orally Administered Drug Products for the Treatment of Fever Blisters

At this time, there is a lack of data from adequate and well-controlled, double-blind studies to establish that lysine (lysine hydrochloride), *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, or any other ingredients are effective for oral administration to treat fever blisters. The agency has proposed the use of topically applied OTC skin protectant or external analgesic drug products as the only current effective OTC treatment for relief of discomfort of fever blisters. The agency published its notices of proposed rulemaking for those classes of OTC drug products in the **Federal Register** of January 31, 1990 (55 FR 3362 and 3370, respectively).

The agency has determined that no orally administered active ingredient has been found to be generally recognized as safe and effective for OTC use for the treatment of fever blisters. Therefore, all orally administered active ingredients for the treatment of fever blisters, including but not limited to lysine (lysine hydrochloride), *Lactobacillus acidophilus*, and *Lactobacillus bulgaricus* that were reviewed by the Panel and the agency, are considered nonmonograph ingredients and misbranded under section 502 of the act (21 U.S.C. 352) and are new drugs under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR Part 314 of the regulations is required for marketing. In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application. Any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 25156 at 25158). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC orally administered drug products for the treatment of fever blisters, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96-354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC orally administered drug products for the treatment of fever blisters is not expected to pose such an impact on small businesses because only a limited number of products are affected. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512-516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b-360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b-263n).

2. New § 310.537 is added to subpart E to read as follows:

§ 310.537 Drug products containing active ingredients offered over-the-counter (OTC) for oral administration for the treatment of fever blisters and cold sores.

(a) L-lysine (lysine, lysine hydrochloride), *Lactobacillus acidophilus*, and *Lactobacillus bulgaricus* have been present in orally administered OTC drug products to treat fever blisters and cold sores. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other orally administered ingredients for OTC use to treat or relieve the symptoms or discomfort of fever blisters and cold sores. Based on evidence currently available, any OTC drug product for oral administration containing ingredients offered for use in treating or relieving the symptoms or discomfort of fever blisters and cold sores cannot be generally recognized as safe and effective.

(b) Any OTC drug product for oral administration that is labeled, represented, or promoted to treat or relieve the symptoms or discomfort of fever blisters and cold sores is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product for oral administration labeled, represented, or promoted for OTC use to treat or relieve the symptoms or discomfort of fever blisters and cold sores is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After December 30, 1992, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Dated: June 17, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

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